Reconsideration is requested of the rejection under 35 USC 112, second paragraph. The multi-dependent claims are deleted, misspellings corrected, and the wording of the claims revised to address the instances of alleged indefinite language set forth in the statement of rejection with respect to the second paragraph of 35 USC 112. Reconsideration is requested of the rejection under 35 USC 112, first paragraph. The following discussion explains how the statement of rejection clearly confuses the field of gene therapy and the field of antisense therapy.

Gene therapy covers methods wherein genes (nucleotides of several hundreds of thousand bases) are delivered into a cell. Delivery is achieved by the use of vectors such as retroviruses, and adeno-viruses, plasmid liposome-complexes, see for example Crystal (cited by the Examiner). Defending on the vector, these nucleotides may be integrated into the target cell genome. The expression product of the newly integrated gene achieves a therapeutic effect. Selection of the vector is crucial; see, for example, Verma et al cited by the Examiner.

In contrast thereto, antisense therapy is directed to the delivery of small nucleic acids (about 10 to 30 nucleotides). Due to the smaller size of these nucleotides, they are able to enter the cells without the need of vectors. Effects are achieved by specific binding of the antisense nucleotides to DNA or RNA in the cell, thus inhibiting expression of the natural gene products.

In the field of antisense therapy, delivery of the small nucleotides is not a real problem. It is more difficult to identify effective antisense molecules, see Branch cited by the Examiner. The present invention is directed to a method to produce antisense oligonucleotides having a reduced toxicity and less unspecific effects.

In contrast to the Examiner's allegation, a person skilled in the art is aware of treatment conditions and modes of delivery of antisense oligonucleotides to organisms.

Reconsideration is requested of the rejection under 35 USC 103(a).

The presently claimed invention is based on the discovery that antisense oligonucleotides are less toxic and/or more effective if the content of elements or residues forming 3 hydrogen bonds to cytosine bases (that is especially "G" or "!") follows certain rules. To facilitate the explanation, the following rules are explained with reference to "G". The rules are:

- the oligonucleotide comprises at least 8 nucleotides
- it comprises at maximum 12 G
- the oligonucleotide does not contain the sequence "GGGG"
- the oligonucleotide does not contain two or more of the sequences "GGG"
- the percentage of residues forming 3 hydrogen bonds is at least 29% of the total number of the nucleotides in the oligonucleotide.

The preferred embodiments are directed to modified oligonucleotides.

According to the Examiner, the claims are obvious in view of Milner et al and James in view of Vaerman et al and Ehrlich et al.

Milner et al teach a method for identifying antisense oligonucleotides showing increased heteroduplex yield. The method is highly empirical. Nearly 2000 oligonucleotides were synthesized and tested for the heteroduplex yield. As it is acknowledged by the Examiner, Milner discloses a method for selecting effective antisense oligonucleotides. Milner et al do neither disclose any teaching that the "G" or "!" content of the oligonucleotide is relevant, nor disclose the rules of claim 1.

James reviews the progress in the field of antiviral antisense nucleic acids. Whereas the present invention is directed to antisense oligonucleotides, James is directed to the use of

endogenously synthesized antisense RNA (see page 194, left column lines 1 to 4), i.e., the effective oligonucleotide is synthesized in the cell. James describes a method that is closer to gene therapy than to antisense therapy. According to page 198 starting from the heading "The size, structure and location of inhibitory antisense RNAs" it becomes clear that the antisense RNAs used by James are large molecules covering 1000 bases (at least 50 bases) being much larger than antisense oligonucleotides.

Despite the fact that James is directed to a different field of therapy, James does not teach that the content of residues forming 3 hydrogen bonds to cytosine (i.e., "G" and "1") should follow certain rules. This is acknowledged by the Examine on page 10, lines 1 and 2 of the Office action.

To overcome this deficiency, the Examiner relied on Vaerman et al. First of all, Vaerman was published on July 1, 1997 that is after the priority date of the present application and should therefore not be relevant. Nevertheless, Vaerman does not teach in the direction of the present invention. According to Vaerman, the oligonucleotides are cleaved by exonucleases to release d-NMPs from the 3'-end (see page 336, left column, 3rd paragraph). Vaerman observed that d-AMP, d-GMP and TMP are cytotoxic in contrast to d-CMP. It may be concluded from this information that the effect of oligonucleotides depends only on the content of "C" at one of the two most terminal 3'-position (see page 334, right column, last three lines).

In contrast thereto, the present invention teaches a different mechanisms for selecting effective oligonucleotides. It does not depend on the content of "C" at the 3'-end. For example, sequence TGF-β 1-3 (SEQ ID NO: 43) has a "CC" at the 3'-end, whereas TGF-β-4 (SEQ ID NO: 44) has not; both are effective and nontoxic. N10 (SEQ ID NO: 11) has a "CC", whereas N11 (SEQ ID NO: 12) has not, both are ineffective or toxic. Clearly, the present invention discloses a different

method for preparing 'good' antisense oligonucleotides than Vaerman. The present invention discloses different effects or rueos for the construction of oligonucleotides than Vaerman. Whereas Vaerman teaches that the number of "C" residues at the 3' terminal end is relevant for the effectiveness of oligonucleotides, the present invention teaches that the overall content of "G" and similar residues such as "I" is relevant and especially elements such as "GGG" and "GGG" should be avoided or reduced.

The Examiner further relied on Ehrlich et al. Ehrlich et al investigated the effect of partially phosphorothioated antisense oligonucleotides. As stated above, the use of modified, e.g., phosphorothioated oligonucleotides is known in the art. The presently claimed invention is directed to a method for preparing more effective oligonucleotides, by selecting better sequences for the oligonucleotides. The use of phosphorothioated oligonucleotides is a preferred embodiment because of the known stability of these oligonucleotides. This may be considered to be not inventive per se.

Ehrlich et al do not give any information that the number of nucleotides such as "G" especially the number of "runs" of "G" such as "GGGG" and "GGG" are relevant for the effectiveness of antisense oligonucleotides. Ehrlich et al only disclose the effect of phosphorothioates.

Starting from page 10, last paragraph, the Examiner summarizes the obviousness rejection. According to the Examiner, Milner et al and James teach methods for selecting effective antisense sequences in target genes. The present invention is also directed to a method for selecting effective antisense sequences but in contrast to Milner et al not to an empirical method but by a prediction of the effectiveness and toxicity of sequences by the rules taught by the invention.

The Examiner further relied on the fact that antisense oligonucleotides exert the effects in both are nonspecific and a sequence specific way. This is correct. Vaerman teaches that toxicity relates to the cytosine content at the 3'-end of the oligonucleotides, whereas the present invention teaches that the content and the position of residues such as "G" and "I" are relevant. In contrast to the argument of the Examiner on page 11, line 2, the present invention doe snot teach to reduce the number of consecutive cytosine residues but to reduce the number of consecutive "G" or "I" residues. None of the cited documents discloses any teaching that discloses or renders obvious a relation between the number of residues such as "G" or "I" and especially a relation to runs such as "GGGG" or "GGG".

Therefore, for the foregoing reasons, the presently claimed invention is nonobvious over the cited references, taken alone or in combination.

Favorable action is requested.

Respectfully submitted,

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